

## Process for generating singlet oxygen and use thereof

The only singlet oxygen oxidation ( $^1\text{O}_2\text{-Ox}$ ) which is currently carried out industrially is the photochemical  $^1\text{O}_2\text{-Ox}$  in which the  $^1\text{O}_2$  is generated by a photochemical route. The disadvantage of this process is the high cost of the photochemical equipment required, and also a limited service life. The lamps required degenerate relatively rapidly during the oxidation as a result of the glass surface becoming dirty. In addition, this process is not suitable for colored substrates. The process is actually suitable only for fine chemicals which are produced on a relatively small scale. (La Chimica e l'Industria, 1982, Vol. 64, page 156)

For this reason, attempts have been made to find other process variants for the  $^1\text{O}_2\text{-Ox}$  which are suitable for the  $^1\text{O}_2\text{-Ox}$  of non-water-soluble, hydrophobic organic substrates.

J. Am. Chem. Soc., 1968, **90**, 975 describes, for example, the classical "dark"  $^1\text{O}_2\text{-Ox}$  in which  $^1\text{O}_2$  is generated not photochemically, but chemically. In this process, hydrophobic substrates are oxidized by means of a hypochlorite/ $\text{H}_2\text{O}_2$  system in a solvent mixture of water and organic solvent. However, this process has found only a few synthetic applications since many substrates are only sparingly soluble in the required medium. Furthermore, the potential use is somewhat limited due to secondary reactions between hypochlorite and substrate or solvent. Furthermore, a large part of the  $^1\text{O}_2$  is deactivated in the gas phase. In addition, this process is not suitable for the industrial scale since attachment of the hypochlorite onto  $\text{H}_2\text{O}_2$  is brought about in the organic medium, and a large excess of  $\text{H}_2\text{O}_2$  is required to suppress the secondary reaction of substrate with hypochlorite. An additional disadvantage arises as a result of the formation of stoichiometric amounts of salt.

One variant of the "dark"  $^1\text{O}_2\text{-Ox}$  which is not based on hypochlorite and thus should partly avoid the above disadvantages is known, for example, from J. Org. Chem., 1989, **54**, 726 or J. Mol. Cat., 1997, **117**, 439, according to which some water-soluble

organic substrates are oxidized with  $\text{H}_2\text{O}_2$  and a molybdate catalyst in water as solvent. According to Membrane Lipid Oxid. Vol. II, 1991, 65, the  $^1\text{O}_2$ -Ox of water-insoluble, organic substrates with the molybdate/ $\text{H}_2\text{O}_2$  system is difficult since it was assumed that none of the customary solvents is suitable for maintaining the disproportionation, catalyzed by molybdate, of  $\text{H}_2\text{O}_2$  into water and  $^1\text{O}_2$ . The use of molybdenum catalysts, however, also has other disadvantages. For example, as well as catalyzing the  $\text{H}_2\text{O}_2$  disproportionation, they also catalyze other undesired oxidations of some substrates. Allyl alcohols, for example, cannot be effectively peroxidized with the molybdate/ $\text{H}_2\text{O}_2$  system since this substance group is epoxidized by molybdenum in the presence of  $\text{H}_2\text{O}_2$ . A further disadvantage of these catalysts is the relatively low pH range in which they function. These catalysts can only be used in the basic range between pH 9 and pH 12; the use of this system is accordingly unsuitable for acidic conditions.

A further way of chemically generating  $^1\text{O}_2$  is, for example, the heating of triphenyl phosphite ozonide, which is obtained from triphenyl phosphite and ozone. A disadvantage of this method is that it is necessary to work at very low temperatures, with the ozonide first being formed and then decomposed by heating to liberate  $^1\text{O}_2$ . However, as is described, for example, in J. Org. Chem., Vol. 67, No 8, 2002, page 2418, this method is only used for mechanism studies since triphenyl phosphite is an expensive and also hazardous chemical.

During the base-catalyzed disproportionation of peracids, further reactive compounds are formed as well as  $^1\text{O}_2$ , which lead to by-products.

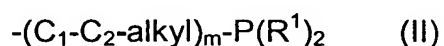
Accordingly, it was an object of the present invention to find a way of generating  $^1\text{O}_2$  while avoiding the above disadvantages.

Unexpectedly, this object was achieved by the use of ozone and a ferrocene compound.

Accordingly, the present invention provides a process for generating  $^1\text{O}_2$ , which comprises treating a ferrocene derivative of the formula



in which Fc is a ferrocene optionally substituted by dimethylaminoethyl,  $\text{C}_1\text{-C}_{12}$ -alkyl, aryl or carboxyalkyl, n may be 1 or 2 and X is a radical of the formula



where m may be 0 or 1 and  $\text{R}^1$  is phenyl, cyclohexyl, tert-butyl, ethyl, isopropyl, methyl, methoxy, ethoxy, phenoxy or butoxy, in an organic solvent at a temperature of from  $-80^\circ\text{C}$  to  $+20^\circ\text{C}$  with 1 to 4 mol of ozone per mole of ferrocene compound, as a result of which  $^1\text{O}_2$  forms.

In the process according to the invention,  $^1\text{O}_2$  is generated by the reaction of a ferrocene derivative of the formula (I) with ozone.

In the formula (I), Fc is ferrocene. The ferrocene derivative is then mono- or di-substituted by a radical of the formula (II)  $-(\text{C}_1\text{-C}_2\text{-alkyl})_m\text{-P}(\text{R}^1)_2$ .

In the formula (II), m is 0 or 1.  $\text{R}^1$  may be phenyl, cyclohexyl, tert-butyl, ethyl, isopropyl, methyl, methoxy, ethoxy, phenoxy or butoxy.

Where appropriate, the ferrocene may also be substituted by further radicals, for example by dimethylaminoethyl,  $\text{C}_1\text{-C}_{12}$ -alkyl, aryl or carboxyalkyl.

For the process according to the invention, both chiral and achiral ferrocene compounds of the formula (I) are suitable.

Examples of suitable ferrocene compounds of the formula (I) are 1,1'-bis(diphenylphosphino)ferrocene, (S,R)-1-(1-dimethylaminoethyl)-1',2-bis(diphenyl-

phosphino)ferrocene, (R,R)-1-(1-dimethylaminoethyl)-1',2-bis(diphenylphosphino)-ferrocene, (S,S)-1-(dicyclohexylphosphino)-2-[1-(diphenylphosphino)ethyl]ferrocene, (S,S)-1-(dicyclohexylphosphino)-2-[1-(dicyclohexylphosphino)ethyl]ferrocene, (R,R)-1-(dicyclohexylphosphino)-2-[1-(dicyclohexylphosphino)ethyl]ferrocene, (R,R)-1-(dicyclohexylphosphino)-2-[1-(diphenylphosphino)ethyl]ferrocene, (R,R)-1-[1-di-tert-butylphosphino)ethyl]-2-(diphenylphosphino)ferrocene, (R,R)-1-[1-(dicyclohexylphosphino)ethyl]-2-(diphenylphosphino)ferrocene, etc.

The ferrocene compound is dissolved in an organic solvent. Suitable solvents here are ethyl acetate, butyl acetate, methanol, ethanol, dichloromethane, cyclohexane, hexane, or acetic acid.

Preference is given to using dichloromethane.

The mixture is then cooled to from  $-80^{\circ}\text{C}$  to  $+20^{\circ}\text{C}$ , preferably to from  $-50^{\circ}\text{C}$  to  $0^{\circ}\text{C}$ , and ozone is introduced.

Ozone is added in the process according to the invention in an amount of from 1 to 4.0 mol per mole of ferrocene derivative. Preference is given to using 1 to 2 equivalents of ozone.

The  $^1\text{O}_2$  which forms is then used for the oxidation of organic substrates which react with  $^1\text{O}_2$ .

The present invention accordingly further provides for the use of the  $^1\text{O}_2$  generated by the ferrocene compounds listed above for the oxidation of organic substrates which react with  $^1\text{O}_2$ .

This may take place according to the invention by metering in a solution of the corresponding substrate during the reaction of the ferrocene derivative with ozone. The metering preferably takes place continuously in this case.

Suitable solvents for the substrate here are, in turn, ethyl acetate, butyl acetate, methanol, ethanol, dichloromethane or acetic acid.

Preference is given to using dichloromethane.

Preference is given to using the solvent which is also used for dissolving the ferrocene derivative.

Where necessary, excess ozone is then blown out, for example by flushing with argon or nitrogen, and the reaction solution which remains, which comprises the oxidation product, is worked up.

However, the substrate solution may also be added only after the ferrocene derivative has reacted with ozone and any excess ozone has finally been removed.

If the reaction of the ferrocene derivative with ozone takes place at relatively low temperatures (e.g.  $-80^{\circ}\text{C}$ ), then the reaction solution treated with the substrate solution can optionally be heated, for example to  $-10^{\circ}\text{C}$ .

The reaction solution which comprises the oxidation product is worked up by customary methods, such as, for example, reduction by evaporation, extraction, drying and isolation of the oxidation product, for example by column chromatography. The ferrocene derivative can be separated off by means of membrane technology.

As organic substrates which react with  $^1\text{O}_2$  it is possible to use the following compounds: olefins which contain one or more, i.e. up to 10, preferably up to 6, particularly preferably up to 4, C=C double bonds; electron-rich aromatics, such as  $\text{C}_6\text{-C}_{50}$ , preferably up to  $\text{C}_{30}$ , particularly preferably up to  $\text{C}_{20}$ , phenols, polyalkylbenzenes, polyalkoxybenzenes; polycyclic aromatics having 2 to 10, preferably up to 6, particularly preferably up to 4, aromatic rings; sulfides, such as, for example, alkyl sulfides, alkenyl sulfides, aryl sulfides which are either mono- or disubstituted on the sulfur atom, and also heterocycles with an O, N or S atom in the ring, such as, for example,  $\text{C}_4\text{-C}_{50}$ , preferably up to  $\text{C}_{30}$ , particularly preferably up to  $\text{C}_{20}$ , furans,  $\text{C}_4\text{-C}_{50}$ , preferably up to  $\text{C}_{30}$ , particularly preferably up to  $\text{C}_{20}$ , pyrroles,  $\text{C}_4\text{-C}_{60}$ , preferably up to  $\text{C}_{30}$ , particularly preferably up to  $\text{C}_{20}$ , thiophenes.

The substrates can here have one or more substituents, such as halogen (F, Cl, Br, J), cyanide, carbonyl groups, hydroxyl groups, C<sub>1</sub>-C<sub>50</sub>, preferably up to C<sub>30</sub>, particularly preferably up to C<sub>20</sub>, alkoxy groups, C<sub>1</sub>-C<sub>50</sub>, preferably up to C<sub>30</sub>, particularly preferably up to C<sub>20</sub>, alkyl groups, C<sub>6</sub>-C<sub>50</sub>, preferably up to C<sub>30</sub>, particularly preferably up to C<sub>20</sub>, aryl groups, C<sub>2</sub>-C<sub>50</sub>, preferably up to C<sub>30</sub>, particularly preferably up to C<sub>20</sub>, alkenyl groups, C<sub>2</sub>-C<sub>50</sub>, preferably up to C<sub>30</sub>, particularly preferably up to C<sub>20</sub>, alkynyl groups, carboxylic acid groups, ester groups, amide groups, amino groups, nitro groups, silyl groups, silyloxy groups, sulfone groups, sulfoxide groups. In addition, the substrates may be substituted by one or more NR<sup>1</sup>R<sup>2</sup> radicals in which R<sup>1</sup> or R<sup>2</sup> may be identical or different and are H; C<sub>1</sub>-C<sub>50</sub>, preferably up to C<sub>30</sub>, particularly preferably up to C<sub>20</sub>, alkyl; formyl; C<sub>2</sub>-C<sub>50</sub>, preferably up to C<sub>30</sub>, particularly preferably up to C<sub>20</sub>, acyl; C<sub>7</sub>-C<sub>50</sub>, preferably up to C<sub>30</sub>, particularly preferably up to C<sub>20</sub>, benzoyl, where R<sup>1</sup> and R<sup>2</sup> can also together form a ring, such as, for example, in a phthalimido group.

Examples of suitable substrates are: 2-butene; isobutene; 2-methyl-1-butene; 2-hexene; 1,3-butadiene; 2,3-dimethylbutene;  $\Delta^{9,10}$ -octalin, 2-phthalimido-4-methyl-3-pentene; 2,3-dimethyl-1,3-butadiene; 2,4-hexadiene; 2-chloro-4-methyl-3-pentene; 2-bromo-4-methyl-3-pentene; 1-trimethylsilylcyclohexene; 2,3-dimethyl-2-butenyl *para*-tolyl sulfone; 2,3-dimethyl-2-butenyl *para*-tolyl sulfoxide; *N*-cyclohexenylmorpholine; 2-methyl-2-norbornene; terpinolene;  $\alpha$ -pinene;  $\beta$ -pinene;  $\beta$ -citronellol; ocimene; citronellol; geraniol; farnesol; terpinene; limonene; *trans*-2,3-dimethylacrylic acid;  $\alpha$ -terpinene; isoprene; cyclopentadiene; 1,4-diphenylbutadiene; 2-ethoxybutadiene; 1,1'-dicyclohexenyl; cholesterol; ergosterol acetate; 5-chloro-1,3-cyclohexadiene; 3-methyl-2-buten-1-ol; 3,5,5-trimethylcyclohex-2-en-1-ol; phenol, 1,2,4-trimethoxybenzene, 2,3,6-trimethylphenol, 2,4,6-trimethylphenol, 1,4-dimethylnaphthalene, furan, furfuryl alcohol, furfural, 2,5-dimethylfuran, isobenzofuran, dibenzyl sulfide, (2-methyl-5-*tert*-butyl)phenyl sulfide etc.

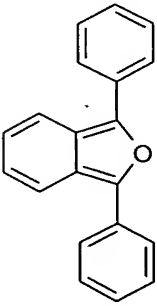
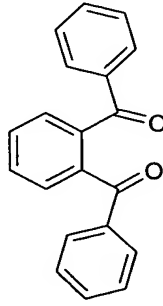
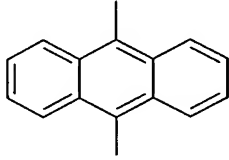
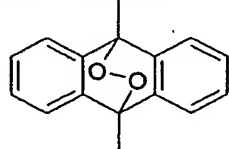
As a result of the oxidation according to the invention, the substrates produce the corresponding oxidation product. Alkenes, (polycyclic) aromatics or heteroaromatics give, in particular, hydroperoxides, peroxides, alcohols or ketones.

As a result of the process according to the invention,  $^1\text{O}_2$  is generated in a simple and efficient manner. A further advantage of the process is that no water is formed during the reaction.

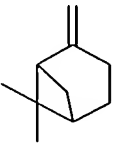
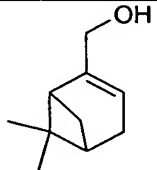
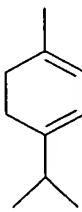
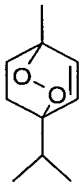
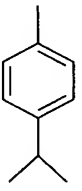
**Examples 1-4:** Generation of singlet oxygen by means of ozone and 1,1'-bis-(diphenylphosphino)ferrocene

0.67 g (1.2 mmol) of 1,1'-bis(diphenylphosphino)ferrocene were taken up in 50 ml of dichloromethane and cooled to  $-20^{\circ}\text{C}$ . 6 g of  $\text{O}_3/\text{m}^3$  (gas flow  $0.06 \text{ m}^3$ ) were introduced into this solution for 9.5 minutes. The substrate was taken up beforehand in 15 ml of dichloromethane and continuously metered in during the ozonolysis. When the absorption of ozone was complete, the reaction mixture was evaporated down to 1/3 of the original volume and filtered off from the precipitated ferrocene derivative, and the resulting filtrate was evaporated to dryness. The results are summarized in Table 1 below.

Table 1:

Substrate	Substrates [mg]	Conversion [%]	Yield [%]	Product
 1,3-Diphenylisobenzofuran	163.0	63.8	62.4	 1,2-Dibenzoylbenzene
 9,10-Dimethylantracene	123.5	15.7	12.4	 9,10-Dimethylantracene endoperoxide



 $\beta$ -Pinene	81.7	5.1	0.4	 Myrtenol
 $\alpha$ -Terpinene	87.6	83.6	7.6 28.0	<div style="display: flex; justify-content: space-around; align-items: center;"> <div style="text-align: center;">             Ascaridole         </div> <div style="text-align: center;">             p-Cymene         </div> </div>

**Example 5:** Generation of singlet oxygen by means of ozone and 1,1'-bis(diphenylphosphino)ferrocene at  $-10^{\circ}\text{C}$ .

7.0 g of 1,1'-bis(diphenylphosphino)ferrocene were dissolved in 160 ml of dichloromethane and cooled in a batch ozonolysis apparatus to  $-10^{\circ}\text{C}$ . This solution was treated at  $-10^{\circ}\text{C}$  with two equivalents of ozone. During the ozonolysis, 1.78 g of  $\alpha$ -terpinene in 20 ml of dichloromethane were continuously metered into the reaction solution by means of a perfuser pump. Excess ozone was then blown out by flushing the apparatus with argon. The reaction solution was evaporated down.

Firstly, the ferrocene phosphate was separated off from the residue obtained by means of column chromatography. For this purpose, 150 g of silica gel 60A were used as the stationary phase, and a 9:1 mixture of n-hexane:MTBE was used as the mobile phase.

The eluate was evaporated down, as a result of which a yellow oil was obtained as residue.

The singlet oxidation product (ascaridole) was isolated from the oil obtained by column chromatography. For this purpose, 50 g of silica gel 60A were used as the

stationary phase, and a 9:1 mixture of n-hexane:MTBE was used as the mobile phase.

The combined fractions which comprised ascaridole were evaporated down, giving a yellow, oily product. The product was characterized by means of H-NMR and thin-layer chromatography.

**Yield:** 75 mg of ascaridole (25% of theory).